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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,371	MORTEN, JOHN EN	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-119* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on January 22, 2003 has been entered. All previous grounds of rejection not reiterated herein are hereby withdrawn. This application contains new grounds of rejection and is made non-final.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-119 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for general methods of sequencing the VCAM-1 gene, does not reasonably provide enablement for methods for diagnosing VCAm-1 ligand mediated disease, methods of detecting specific polymorphisms in the VCAM-1 gene, methods of genotyping VCAM-1 by detecting specific polymorphisms or allele specific primers or probes for VCAM-1 polymorphisms. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.
The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to methods for evaluating a human for being at risk for a VCAM-1 mediated disease wherein said methods comprise detecting the presence of a polymorphism in the human VCAM-1 gene at position 278, 647, 707, 748, 829 or 1467 and determining that an individual is at risk of developing a VCAM-1 related disease based on the presence of said polymorphism. The specification teaches that 5 of the polymorphisms are present in the promoter region of VCAM-1 (the 6th being in a sequence upstream of the silencer region) and that the polymorphisms alter known transcription factor binding sequences (see, for example, pages 14-15). The specification also teaches that VCAM-1 expression on unactivated vascular endothelial cells is low or absent but is upregulated in human inflammatory diseases such as rheumatoid arthritis, multiple sclerosis, allergic asthma and atherosclerosis. However, the specification does not teach that an alteration at any of the specified nucleotide positions alters expression of VCAM-1.

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the state of the art indicates that diagnosing a disease based on the presence of a polymorphism is highly unpredictable in the absence of any evidence showing an association between that polymorphism and the disease or the polymorphism and expression levels of a gene associated with the disease. In particular, the specification (pages 6-7) suggests that the disclosed polymorphisms can be used to diagnose disease, or can be used to develop drugs for the treatment of diseases or can be used to evaluate the efficacy of therapeutic compounds. However, the specification has not clearly taught an association between the disclosed VCAM-1 polymorphisms and the occurrence of disease. Therefore, it is clear that further research would be required to practice the claimed methods and to use the disclosed polymorphisms because this would require identifying a disease which is correlated with the presence of the VCAM-1 polymorphisms. While 5 of the

polymorphisms are in a silencer region, it is highly unpredictable as to whether these polymorphisms will alter the expression of VCAM-1. There is no evidence to suggest that the stated polymorphisms occur at positions within the silencer region which are critical to the function of the silencer region. There is also no guidance provided in the specification to indicate whether one or both alleles must be altered in order for their to be an effect on VCAM-1 expression that leads to the occurrence of a disease associated with VCAM-1 ligand mediated disease. One would not expect that every single nucleotide within the span of nucleotides 540-1892 of the 5' end of the promoter region would be critical to the functioning of the silencer region. It is further unpredictable as to whether a polymorphism upstream of a silencer region will have any effect on the expression of VCAM-1. It is well accepted that polymorphisms frequently occur in non-coding sequences and the effect of such an alteration can only be determined by specifically assaying a polymorphism and determining whether such a polymorphism causes an increase or decrease in expression. It is unpredictable as to whether a base pair change within even a regulatory sequence will effect the activity of that regulatory sequence. Some alterations in a nucleotide sequence may enhance the binding of a regulatory factor, while others decrease the binding of the regulatory factor and yet still others do not effect the binding of a regulatory factor. This unpredictability in the art is supported by the teachings of Minami (Journal of Biological Chemistry (2001) 276:47632-47641) which teaches that while the VCAM-1 gene contains a consensus Thrombin Consensus Element (TRE) in the promoter region, mutation of this TRE element does not affect VCAM-1 expression. Furthermore, Taylor (Blood (2002) 100:

4303-4309) analyzed 6 polymorphisms in the VCAM-1 silencer region and did not find an association between any of these polymorphisms and the occurrence of stroke in sickle cell anemia populations. Taylor reported only an association between the presence of one of the polymorphisms at –1599 of VCAM1 and WBC cell levels in sickle cell stroke patients versus controls. These results highlight the unpredictability in determining whether an alteration in a regulatory sequence will effect expression of VCAM-1 and whether such an alteration will be associated with disease. The results also emphasize the fact that the findings associated with one polymorphism do not necessarily extend to all other polymorphisms in a given region. Furthermore, it is noted that the specification does not exemplify any methods in which a VCAM-1 ligand mediated disease is diagnosed by detecting one of the stated polymorphisms. Even if the specification were to show that one polymorphism is associated with a particular disease, this would not provide enablement for each of the additional polymorphisms or for all VCAM-1 mediated diseases. VCAM-1 mediated diseases include a multitude of diseases that are not necessarily dependent on an increase in expression of VCAM-1 in a tissue in which VCAM-1 expression is low or absent due to the presence of the silencer region. For example, the specification discusses diseases that are associated with increased soluble levels of VCAM-1. The specification has not established that any of the claimed polymorphisms are associated with increased soluble levels of VCAM-1.

The specification teaches that the claimed methods of detecting a polymorphism and determining the genotype of a VCAM-1 gene are to be used to diagnose risk of developing or having a VCAM-1 ligand mediated disease. While general methods are

known in the art for sequencing genes and promoter regions, the specification has not shown that any particular polymorphisms in the promoter or intron regions are associated with VCAM-1 mediated diseases. Accordingly, the specification has not taught one of skill in the art how to use the broadly claimed methods for any practical purpose other than to determine the sequence of the VCAM-1 gene.

RESPONSE TO ARGUMENTS:

In the response of August 22, 2003, Applicants traversed the previous grounds of rejection by stating that "anyone having ordinary skill in the would appreciate the potential of any of the polymorphisms to disrupt the regulated expression of VCAM-1, thereby leading to misexpression of VCAM-1 protein and subsequent disease in a human." Applicants state that the disclosed polymorphisms interrupt predicted consensus binding sites and thereby these polymorphisms "would at the very least flag an individual as being one who is at risk for a VCAM-1 mediated disease." Applicants arguments have been fully considered but are not convincing because there is no evidence of record to establish that an alteration in a silencer region 1 or that a change in a sequence upstream from the silencer region necessarily results in a change in the expression pattern of VCAM-1. Not all consensus binding sequences within a silencer region will be important in the functioning of the silencer region and not all changes within consensus sequences will effect the expression of VCAM-1. It is unpredictable as to which if any of these alterations actually effect VCAM-1 expression and which if any are associated with a "VCAM-1 ligand mediated disease." In the absence of any data showing an association with disease or an association with expression levels, the

finding of a polymorphism in the silencer region spanning nucleotides –288 to –1641 of VCAM-1 would not lead one of ordinary skill in the art to conclude that such a polymorphism would be diagnostic of disease.

3. Claim 18-22, 72-76, 98-102 and 118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not provide basis for the amendment to the claims to include methods and primers/probes for detecting a VCAM-1 ligand mediated disease wherein the VCAM-1 mediated is inflammatory bowel disease, contact dermatitis, insulin-dependent diabetes, glomerulonephritis or transplant rejection. The specification as originally filed states that a VCAM-1 ligand mediated disease may include multiple sclerosis, rheumatoid arthritis, atherosclerosis and allergic asthma (see page 1 of the specification, lines 4-7). It is noted that the response of August 22, 2003 states that support for this amendment may be found at page 2 lines 9-12. However, page 2 of the specification teaches only that monoclonal antibodies against the alpha4-integrin subunit have been found to be effective in human inflammatory diseases, such as multiple sclerosis, rheumatoid arthritis, allergic asthma, contact dermatitis, transplant rejection, insulin-dependent diabetes, inflammatory bowel disease and glomerulonephritis. The specification does not teach that the generic

recitation of "VCAM-1 ligand mediated diseases" is intended to include the specific diseases of inflammatory bowel disease, contact dermatitis, insulin-dependent diabetes, glomerulonephritis or transplant rejection or that the presence of the stated polymorphisms is associated with each of these diseases.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-31, 33, 77, and 92-119 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-31 are indefinite and vague because the claims do not clarify the relationship between identifying a SNP and diagnosing a VCAM-1 ligand mediated disease. The claims recite a step of identifying a SNP and a step of diagnosing a VCAM-1 ligand mediated disease but do not clarify how the one diagnosis the disease. That is, is the information regarding the identity of the SNP used to diagnose the disease?

Claims 22, 77 and 102 are indefinite because it is not clear as to how the recitation in claim 22 further limits the claim. It is unclear as to whether the human that is being analyzed has already been diagnosed as being at risk of transplant rejection or if the method is one for evaluating whether a human is at risk for having a transplant rejection.

Claim 33 is indefinite because the phrase "the polymorphic position" lacks proper antecedent basis.

Claims 92-118 are indefinite. The claims are drawn to methods for characterizing a genotype, yet recite a final step of recording the identity of a nucleotide. The claims do not clarify how recording the identity of a nucleotide results in the characterization of a genotype. Therefore, it is not clear as to whether the claims are intended to be limited to methods for characterizing a genotype or methods for recording the identity of a nucleotide.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32-76, 78-102, and 104-119 are rejected under 35 U.S.C. 102(b) as being anticipated by lademarco (Journal of Biological Chemistry, 1992).

lademarco et al teaches the sequence of the VCAM-1 promoter region (see figure 3) and primers useful for amplifying sequences of the promoter region (pages 16324-16325). It is noted that the claims require that the primers and probes comprise a polymorphism, e.g. a "C" but do not clearly define the sequences surrounding the polymorphism. The primers and probes are characterized as specifically detecting e.g. a C at position 278, but the primers and probes do not define the nucleotides defining the C. Accordingly, the claims read on the promoter sequences and primers of lademarco which include the individual nucleotides represented by nucleotide positions 278, 647, 707, 748, 829 and 1467 of SEQ ID NO: 2. The primers of lademarco are

considered to be allele specific because they hybridize to an allele of the VCAM-1 gene and are capable of indirectly detecting the stated polymorphisms since they amplify sequences of the promoter region containing these polymorphisms. Furthermore, the promoter sequence disclosed by lademarco is considered to be an allele specific probe and primer because it hybridizes to a specific allele of VCAM-1 and it can be used to detect polymorphisms in VCAM-1 by, for example, SSCP. Using methods known in the art, such as SSCP, the nucleic acids of lademarco can be used to distinguish between, e.g., a C and a T at position 278 of SEQ ID NO: 2. The promoter sequence is also considered to constitute a primer because it an be extended at its 3' end. With respect to claim 62, lademarco also teaches labeling the nucleic acids (see pages 16323-16324).

With respect to claims 66-76, 78-102, 104-119, lademarco (see for example, page 16324) teaches methods of sequencing the promoter region of VCAM-1, which region contains the nucleotides at positions 278, 647, 707, 748, 829 and 1467 of SEQ ID NO: 2. The claims as broadly written include general methods for sequencing the VCAM-1 promoter region. The claims require only performing the method steps of providing a sample of nucleic acid from a human, determining the identity at one or more positions of 278, 647, 707, 748, 829 and 1467 of SEQ ID NO: 2, and recording the identity of the nucleotide. The method of sequencing disclosed by lademarco includes each of these steps. The recitation in the preamble of "characterizing the genotype of a human" does not distinguish the claimed method over that of lademarco because such a recitation does not result in a manipulative difference in the method steps when

compared to the prior art disclosure. Furthermore, the recitation in the claim that the human is "at risk for having a VCAM-1 ligand mediated disease" does not distinguish the claim over the prior art because: 1) the claims do not require performing an actual process in which an individual is identified based on some specified criteria as being at an increased risk of having a VCAM-1 ligand mediated disease as compared to members of a control population; and 2) all members of the population are considered to be at some level of risk of developing some VCAM-1 ligand mediated disease.

6. ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 77 and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over lademarco et al in view of Chan (US Patent No. 6,355,420).

The teachings of lademarco are presented above. lademarco teaches determining the sequence of the VCAM-1 promoter using dideoxy sequencing methods, but does not teach using FRET methods.

Chan (see for example columns 29-30) teaches methods of FRET sequencing.

In view of the teachings of Chan, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have determined the sequence of the VCAM-1 promoter region using FRET sequencing in order to have achieved the

advantages set forth by Chan (e.g., column 1) of providing a more rapid and efficient means for determining the sequence of VCAM-1 nucleic acids.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
September 11, 2003

CARLA J. MYERS
PRIMARY EXAMINER